DEFENSE HEALTH BOARD
FIVE SKYLINE PLACE, SUITE 810
5111 LEESBURG PIKE
FALLS CHURCH, VA 22041-3206

October 4, 2007

DHB

MEMORANDUM FOR: The Assistant Secretary of Defense (Health Affairs)

SUBJECT: Pandemic Influenza Preparedness Recommendations 2007-02

1. References:

   1.1 Memorandum, DASD (FHP&R), 18 May 2007, Force Health Protection for Pandemic Influenza: Risk Management Models for Pre-pandemic Vaccine and Antivirals.

   1.2 Memorandum, DHB Pandemic Influenza Preparedness Subcommittee, 18 July 2006, Recommendation Regarding FDA-Approved, Clade 1, Pre-pandemic Vaccine.

2. At the request of Deputy Assistant Secretary of Defense for Force Health Protection and Readiness (DASD (FHP&R) the Pandemic Influenza (PI) Preparedness Select Subcommittee of the Defense Health Board has developed a series of recommendations regarding the Department of Defense pandemic influenza preparedness and control strategy. These recommendations are hereby submitted to the Defense Health Board for consideration, at a future open meeting of the Board.

3. Specifically, in a May 18, 2007 memorandum, the PI Subcommittee was asked to provide comment on the disposition of the current stockpile of Clade I avian influenza vaccine and the option of offering the vaccine to service members prior to the vaccine's scheduled expiration date in December 2007. The Subcommittee was also asked to provide recommendations on the Department's overall pandemic influenza vaccine procurement strategy, particularly as it relates to ensuring effective vaccine stockpiles to protect the members of the armed forces and in a larger sense support the National Pandemic Influenza Strategic Plan. Additionally, the Subcommittee was asked to provide comment on the possible procurement and expanded use of additional supplies of antiviral medications in the event of an influenza pandemic.

4. The Subcommittee met on May 30 and June 21, 2007 to consider the questions posed by the DASD (FHP&R). In addition to conducting a review of the current literature of avian influenza vaccines, members of the Subcommittee received briefings and comments from representatives of the Department of Defense, the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Department of Health and Human Services. As a result of its deliberations, the Subcommittee puts forth the following recommendations for the Board's consideration:

4.1 *Use of Clade 1 Vaccine*—The Subcommittee recommends that DoD support efforts to extend the shelf life of the currently stockpiled Clade 1 A/H5N1/1203 vaccine.

4.1.1 The Subcommittee reaffirms its recommendations of July 2006 (independent of the issue of vaccine expiration) that Clade 1 vaccine should be offered to persons within DoD at highest risk of occupational exposure to H5N1 viruses, which totals approximately 1,500 individuals. The DoD should collect follow-up safety and immunogenicity data on all individuals receiving this vaccine.

However, given the current level of pandemic influenza risk and the limited data on the Clade 1 vaccine's effectiveness as a primer, the Subcommittee advises against offering Clade 1 vaccine to service members outside of those at highest risk of exposure **at this time**. If additional safety and immunogenicity information becomes available or if the threat of a pandemic increases, the Subcommittee will reconsider this position.

4.1.2 In addition, the Subcommittee recommended that DoD pursue the extension of the vaccine's shelf life (even if it must be retroactively approved by the FDA). The Subcommittee recommends that the DoD and the Department of Health and Human Services (DHHS) immediately engage in discussions with the FDA regarding the data available and required to extend the expiration date of the currently stockpiled Clade 1 vaccine. Because the vaccine expires in December 2007, immediate action is necessary. In this regard the FDA has noted that accelerated stability testing is an acceptable mechanism for extension of expiry dates.

4.2 *Disposition of Clade 1 Vaccine*—Given the Subcommittee's decision to pursue an extension of the shelf life of the currently stockpiled Clade 1 vaccine, the Subcommittee recommends that DoD not dispose of the currently stockpiled Clade 1 vaccine, even after the December 2007 expiration date is reached, as retroactive extension of its expiration date may be possible.

4.3 *Procurement of Influenza Antivirals*—The Subcommittee supports increasing the pre-pandemic antiviral stockpile to allow DoD to expand prophylactic strategies. This includes purchasing two million additional treatment courses of Oseltamivir (20 Million 75 mg tablets), thus doubling the current stockpile. The stockpile would then contain 4 million treatment courses of Oseltamivir.

4.4 *Prophylactic and Therapeutic Strategies*- The Subcommittee recommends further discussion and modeling in order to achieve consensus regarding the optimum balance of **treatment** [75 mg Oseltamivir BID X 5D], **post-exposure prophylaxis** [short-term prophylaxis to exposed close contacts in addition to treating the index patients -- 75 mg Oseltamivir BID X 5D], and **pre-exposure**

prophylaxis [prophylaxis of entire or selected populations at either high risk of disease complications or consisting of essential mission personnel -- 75 mg Oseltamivir daily for 42 days] and the most appropriate target populations, given the likely supply of antivirals and the need to protect mission essential/critical forces.

4.5 *Strategy for Future Vaccine Procurement*—As part of a strategic approach to the procurement of safe and effective vaccines and antivirals against pandemic influenza, as well as a long-term plan for the acquisition of broadly protective pandemic influenza/avian influenza vaccines, the PI Subcommittee has several recommendations, which include reiteration of several recommendations made in our July 2006 memorandum. Specifically:

4.5.1. DoD must be a full partner working effectively and interactively with NIH, CDC and FDA in the national effort to respond to the pandemic influenza/avian influenza threat. During past influenza virus threats (e.g. 1957, 1968, and 1976) DoD was directly involved with the CDC, NIH and FDA in developing and evaluating surveillance and epidemiologic data, vaccine selection and evaluation, evaluation of vaccine immunogenicity and reactogenicity data and the planning of efficacy studies. We are concerned that such partnerships are not currently operative and, consequently, that decisions are being made that may not fully serve the unique needs and responsibilities of DoD. Such partnerships should allow access to the following NIH/FDA/CDC information useful for devising a comprehensive DoD Pandemic Influenza Response and Vaccine Procurement Plan:

4.5.1.1. Data regarding the antigenic and genetic analysis of influenza isolates submitted to the various HHS and DoD laboratories

4.5.1.2 Data regarding clinical trials involving investigational vaccines against human A/H5N1 and any other potential pandemic influenza virus strains:

- A list of vaccines currently being evaluated and candidate vaccines in the pipeline, with information on their availability (dates and quantities)
- A list of completed, planned, pending and in progress clinical studies with initiation and completion dates, and information on study design and on the numbers and ages of the subjects involved
- Data on immunogenicity, safety, dosing, duration of antibody effect, kinetics of antibody response, cross-reactivity against related viral Clades, vaccine potency over time, and priming effects

4.5.1.3 Depending upon timelines and the speed with which the above data can be accumulated, DoD should volunteer as a clinical trial site in an

effort to accelerate the completion of these research efforts and insure that the results are relevant to military populations

5. DoD should develop a comprehensive and informed procurement "business model" for decisions regarding acquisition of pandemic vaccines and other biologics, as well as antiviral medications. For example, a "rolling inventory model" that allows limited purchase and stockpiling of the "best" currently available vaccines, along with possible contract clauses to allow for interim emergency needs for the rapid acquisition of additional pandemic vaccine doses, appears optimal. In addition, such a model would inform and allow the limited purchase and stockpiling of next generation vaccines, without committing the entire vaccine acquisition budget to a single vaccine, and yet allow for sufficient real and virtual supplies to be available in the event that an immediate response (i.e. deliver vaccines) is required.

6. The Subcommittee recommends that the Department adopt a vaccine procurement strategy that both insures the broadest possible influenza subtype coverage and remains economically feasible. The Subcommittee remains impressed by the variety of vaccines in development and thus recommends that the DoD develop a flexible policy regarding vaccine procurement that allows for rapid adjustments in response to the emerging science, without making huge budgetary commitments to any single vaccine at the current time. Furthermore, the Subcommittee recommends that DoD make every possible effort to insure that commitments by DoD to purchase and stockpile large amounts of any specific pre-pandemic influenza vaccine are made only after and on the basis of a review of clinical data on that vaccine's immunogenicity.

7. The Subcommittee recommends that DoD actively develop, fund and sustain a **PI/AI Research and Development Focus** in order to effectively participate in inter-agency efforts against PI/AI. The development of such clinical research capacity and expertise would allow DoD to rapidly and effectively evaluate and disseminate new information in real time, rapidly conduct clinical trials, collect and analyze epidemiologic data, identify candidate vaccines suitable for use in the military, and coordinate DoD response planning. Such a research and development capacity, and the resultant expertise would be reminiscent of the past successes DoD experienced in response to influenza threats during and after World War II with the influenza commissions, and could integrate in a synergistic manner with plans for an Armed Forces Health Surveillance Center.

8 The subcommittee remains concerned with the nearly exclusive reliance of HHS (and thus by default for DoD) on inactivated split or subunit A/H5N1 vaccines as the primary vaccines being developed and evaluated in anticipation of the occurrence of pandemic influenza. While the data are both incomplete and conflicting, past data suggests the *potential* superiority of inactivated whole influenza virus vaccines for primary immunization against new influenza virus subtypes. There is also the possibility that an inactivated whole virus vaccine

might be more efficient than split virus vaccines in priming for new variants within a subtype. Live attenuated vaccines are another promising alternative which should be vigorously pursued. While recognizing the desire of HHS (and DoD) to stockpile pre-pandemic influenza vaccines that can be readily licensed by the FDA, and the reluctance of manufacturers to invest in the production of pre-pandemic influenza vaccines by methods that differ from those used for the annual production of inter-pandemic influenza vaccines, there are several reasons to pursue and accelerate the parallel development and stockpiling of whole virus and live attenuated vaccines:

8.1 There is a long history of the routine use of whole virus vaccines for the prevention of pandemic and inter-pandemic influenza. Whole virus vaccines were used in both military and civilian populations for many years, and numerous studies found them to be safe and effective. The large clinical trials with A/NJ/76(H1N1) vaccines showed that the whole virus vaccine was more immunogenic than split virus vaccine, but was also more reactogenic (Clinical Studies of Influenza Vaccines-1976. *J Infect Dis* 136 Suppl: S435-S693, 1977).

8.2 While the superior immunogenicity of whole virus vaccine for primary immunization is well documented across a range of influenza A subtypes, little data on the A/H5N1 subtypes is available. We note that only one published study of an A/H5N1 whole virus vaccine candidate has been published (Lin et. Al. Safety and immunogenicity of an inactivated adjuvanted whole-virion influenza A (H5N1) vaccine: a phase I randomized controlled trial. Lancet 2006;368:991-97). This whole virus vaccine, even when alum adjuvanted and given as two 10 mcg doses 28 days apart, only induced seropositivity in 78% of high dose recipients. In contrast, a recent publication of a split virus vaccine with a proprietary adjuvant (GSK-ASO3) , administered as two 3.8 μg doses of HA combined with the ASO3 adjuvant induced ≥1:40 HI titers and four-fold increases in neutralization titers in 87% of vaccines. In addition, low-dose ASO3 adjuvanted Clade 1 A/H5N1 vaccine induced cross-reactive neutralizing antibody responses against the Clade 2.1 Indonesia strain in more than 75% of individuals with a GMT 6-fold higher than the non-adjuvanted formulation (Leroux-Roels I, et. Al. Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1prototype pandemic influenza vaccine. Lancet. 2007; in press).

8.2.1 The use of adjuvants appears to be the primary means by which HHS hopes to improve the immunogenicity of the split virus vaccines now being stockpiled. However, the ability of adjuvants to accomplish this remains an unrealized promise, and adjuvants themselves may be reactogenic. In addition, substantial long-term safety data are not presently available for adjuvanted influenza vaccines.

8.2.2 Given the insufficient data available, and the documented historical superiority of whole virus vaccines against novel influenza A strains, the Subcommittee believes it is essential to pursue the development of whole, split, and live-attenuated vaccines in parallel.

9. *Guidelines for Use of Convalescent Plasma Therapy*—The subcommittee recommends that the Department further consider development of guidelines for the use of convalescent and immune plasma for PI and other military-relevant disease threats. A review of the literature from the past pandemics when antivirals were unavailable, as well as considerable evidence from the pre-antimicrobial era, indicates a potential role for convalescent and hyper immune plasma as a possible treatment strategy modalities. Given the well documented ability of influenza A to develop resistance to antivirals, consideration of this strategy and the development of guidelines for its implementation would appear prudent. The most practical and expeditious manner in which to accomplish this is likely to be to convene a working group of subject matter experts in the immune plasma/blood banking fields.

10. The above recommendations were unanimously approved.

FOR THE DEFENSE HEALTH BOARD:

Gregory A. Poland, M.D.
DHB, President
Subcommittee Chairman

Distribution List

DHB Members & Consultants
DASD(C&PP)
DASD(FHP&R)
Surgeon General of the Army
Surgeon General of the Navy
Surgeon General of the Air Force
DASG/ZX
SAAA-DA
Library of Congress